

## Citation:

Harland JJ, Haffner TA. Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol. *Atherosclerosis*. 2008;200(1):13-27

**PubMed ID:** [18534601](#)

## Study Design:

Meta-analysis : Systematic Review

## Class:

M - [Click here](#) for explanation of classification scheme.

## Research Design and Implementation Rating:



**POSITIVE:** See Research Design and Implementation Criteria Checklist below.

## Research Purpose:

- To determine the effect of a daily intake of circa 25g soya protein on blood lipids in adults with normal or mildly elevated cholesterolaemia.

## Inclusion Criteria:

- Publications from January 1995 to September 2007.
- An original RCT, parallel or crossover design, published in a peer reviewed journal and included a suitable (non-soya protein) control treatment.
- Soy protein intake was ca. 25g (range 10-40g) and could be derived from ISP, soya protein concentrates or soya foods.
- Volunteers were healthy or mild hypercholesterolaemic, with weight loss <2 kg/day and average BMI <30 .
- Study duration was a minimum of 4 weeks or one menstrual cycle.

## Exclusion Criteria:

- Duplicate studies.
- No relevant to study question.
- Failed to meet broad inclusion criteria and failure to respond or unavailability of requested information.

## Description of Study Protocol:

### Recruitment

- Medline and other scientific databases (Embase, SciSearch and Current Contents) were searched to identify randomized controlled trials (RCTs); these were systematically reviewed against pre-determined criteria.
- Hand searches of key papers and publications
- Reference lists in identified papers scrutinised for further studies.
- Search terms: SOY(A), CHOLESTEROL or BLOOD LIPIDS
- search confined to human studies, no language restriction
- Systematic review includes eligible RCTs.
- Publications from January 1995 to September 2007.

### Design: meta-analysis and systematic review

- Data were independently extracted by both of us and the key characteristics from RCTs collated, including design: categorized as parallel or crossover, number of volunteers, gender, age, location, duration of study, source and amount of soya protein, blood lipid values and, if available, major nutrient content of diet.

### Blinding used (if applicable)

- Not reported

## Intervention (if applicable)

- Soya protein source and amount on lipid profile: Eligible RCTs evaluated the effect of 25g (range 15-40g) soya protein on measures of blood lipids (total-C, HDL-C, LDL-C, Apo AI and Apo B).

## Statistical Analysis

- Mean and standard deviation (S.D.) of the change in blood lipid values were calculated for intervention and control group at baseline and follow-up.
- Weighted estimates of trial results were combined with a fixed effect approach and 95% confidence intervals (CIs) were calculated and heterogeneity tested by calculating Hodge's and Cohen's coefficients.
- To pool the overall standardized mean effect size, each study was weighted by the reciprocal of the total variance for change in blood lipid levels.
- Additionally meta-regression analysis was conducted with no intercept term to determine the dose response between soya protein and net change in either LDL or HDL (weighting by the inverse of the variance) and in a separate analysis, the effect of baseline cholesterol on net change in LDL or HDL.
- Comprehensive Meta-Analysis software (Biostat, Englewood, NJ 07631, USA) was used for all statistical analysis.
- To examine the effect on various co-variants a number of sub-analyses were conducted to explore the effect of study design, source of protein and gender on the standardized mean difference in LDL and HDL.
- To examine potential publication bias the standard error (S.E.) of the studies were plotted against their corresponding effect size and plotted as funnel plots and the classic fail-safe N-value calculated.

## Data Collection Summary:

### Timing of Measurements

- Publications from January 1995 to September 2007.
- Duration of soy foods and ISP intake: 4-52 weeks (range) to study the effects on lipid profile.

### Dependent Variables

- Mean total cholesterol, LDL, HDL and blood triglycerides, apo A-I and Apo B

### Independent Variables

- Soy protein intake

### Control Variables

## Description of Actual Data Sample:

**Initial N:** 172

**Attrition (final N):** RCTs: 30

**Age:** 27-67 year (range)

**Ethnicity:** Not available

**Other relevant demographics:** Duration : 4-52 weeks (range) ; Jadad score (best quality studies): range 1-5; total cholesterol range : 4.57-7.03 mmol/L.

### Anthropometrics

**BMI:** <30 kg/m<sup>2</sup>

**Location:** Study reported from UK ( used multinational studies for the meta-analysis)

## Summary of Results:

- Studies identified 172 RCTs.
- 30 potential studies were retained for analysis.
- Multiple treatments were selected from 10 studies with the result that 42 treatment arms were compared (n=2913).
- All studies were randomized, 16 of the studies were double-blinded, 14 parallel design and 16 crossover design.
- The main source of soya protein was ISP (17 studies), and in the remaining studies soya foods either of a traditional nature or prepared specifically for the study were used (13 studies).
- Average soya protein intake in the 30 studies was 26.9 g (range 15-40g); study duration was from 4 to 52 weeks; study population average age range was 27-67 years and their baseline total cholesterol range of 4.57-7.03 mmol/L (mean 5.96 mmol/L).
- In studies that reported macronutrient intake; fat intakes were moderate to low, in the range of 27-33% of energy.
- Jadad scores indicated studies of a high caliber, six studies had excellent jadad scores, and average score was 3.5. Studies that included everyday soya foods scored less, as often their design could not accommodate double blinding.
- All trials measured mean change in LDL and HDL from baseline to the longest follow-up point. The 42 treatments arms represented 2913 adult subjects.
- 806 men and 1997 pre, peri and postmenopausal women of which the single largest population group was postmenopausal women (1647).
- Inclusion of soya protein in the diet resulted in a highly significant standardised difference in mean LDL cholesterol of -0.23 mmol/L ( $P<0.0001$ ).
- LDL was lower or unchanged in 38 of the 42 studies, but was statistically significantly lower in only four individual studies.
- Crossover studies resulted in a substantially lower effect (ca. 20%) on LDL. The longer duration of cross over trials leading to study fatigue, compliance issues or incomplete clearance of the preceding treatment may be contributory factors.
- There was increase in HDL cholesterol of 0.071 mmol/L which just failed to reach significance ( $P=0.057$ ). All data were tested for heterogeneity and none identified ( $P>0.10$ ).
- The weighted meta-regression analysis indicated no significant relationship between soya protein intake in the range of 15-40 g and standard mean difference in LDL, point estimate 0.002, intercept 0.228 or HDL point estimate 0.005, intercept -0.089.
- Data for blood triglycerides was available from 39 treatment arms (n=2614); the standardized difference in means was 0.087 mmol/L ( $P=0.004$ ). The standardized difference in mean total cholesterol (41 treatment arms) was 0.22 mmol/L ( $P<0.0001$ ) lower in the soya group; equivalent to 3.7% reduction in baseline values. Heterogeneity was tested in all analyses and none found ( $P>0.10$ ).
- A limited number of studies (N=10) representing 18 treatment arms (n=1611) reported values for either or both Apo A-I and B.
- The pooled data demonstrate that standardized in mean in Apo B of -0.229 g/L,  $P=0.0004$ , compared to the effect on Apo A-I, which was negligibly higher (0.039 g/L).
- There was no effect on Apo A-I, but Apo B was reduced by 0.021 g/L,  $P=0.01$  in the soya group.
- All data were tested for heterogeneity and none identified ( $P>0.10$ ).
- Parallel design studies were compared to crossover design; both LDL and HDL were altered to a greater extent in parallel studies than the group as a whole.
- This was also the case when ISP was compared to soya foods. In both parallel design studies and the ISP sub-group, HDL was significantly increased ( $P<0.05$ ).
- It appears likely that study design is driving the reported difference between soya foods and ISP, as a greater proportion of the ISP studies were of a parallel design.
- Male volunteers resulted in a greater reduction in LDL cholesterol than demonstrated in women, although sample size for this group was relatively small.
- Baseline total cholesterol and standard mean difference in either LDL, point estimate -0.030, intercept 0.410, or HDL, point estimate 0.008, intercept -0.023 and no significant associations were identified.

## Author Conclusion:

- The authors conclude that the systematic review, meta-analysis and meta-regression of studies in adults with normal or mild hypercholesterolemia has demonstrated that the modest amounts of soya protein ( $\leq 25$  g/d), are effective reducing blood total and LDL-C, Apo B and triglycerides.
- The inclusion of modest amounts soya protein (ca. 25g) into the diet of adults with normal or mild hypercholesterolemia resulted in small, highly significant reductions in total and LDL cholesterol, equivalent to ca. 6% LDL reduction.
- This practically achievable intake, particularly when combined with other dietary measures, can make a useful contribution to blood cholesterol management.
- There is also a small beneficial increase in HDL-C, which may be significant in certain sectors of the population.
- This is an opportunity for practitioners and patients alike to capitalize on these advances and promote public health measures that reduce blood cholesterol and CHD risk through dietary approach.

## Reviewer Comments:

- *This is a very clear systematic review and meta-analysis.*
- *The authors conducted meta-analysis on primary and secondary outcomes including subset of analysis of using various study design models.*
- *It is interesting that authors observed that study design is driving the reported difference between soya foods and ISP and greater proportion of the ISP studies were of a parallel design.*
- *Crossover studies, resulted in a substantially lower effect (ca. 20%) on LDL. May be due to longer duration and possible carryover effect.*
- *Based on these interesting results further studies are recommended to see whether soy foods and ISP in cross over /parallel arm study design can produce similar results.*
- *The data is not presented for blood pressure and family history.*
- *Studies also required in young and old men and women to study the effect of soy foods and ISP on metabolic risk factors.*

## Research Design and Implementation Criteria Checklist: Review Articles

### Relevance Questions

1. Will the answer if true, have a direct bearing on the health of patients?

Yes

2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

### Validity Questions

1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issues considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes

*Copyright American Dietetic Association (ADA).*